Diffusion Tensor Tractogrpahy Quantification of Wallerian Degeneration of the Uncinate Fasciculus in Multiple Sclerosis

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Introduction: The noninvasive identification of potential disease mechanisms such as Wallerian degeneration (WD) is needed for diagnostic and therapeutic clinical trials of multiple sclerosis (MS). Diffusion tensor imaging provides several scalar metrics such as anisotropy and diffusivity that were used to identify WD in a host of pathologies with focal or diffuse lesion activity [**1-5**]. Normal appearing whole brain white matter **[4]** or regions of interest from the corpus callosum [**2,5**], and corticospinal tracts were used in previous studies to identify patterns of WD in relation to lesions **[5].** Previous MS studies have not considered association pathways such as the uncinate fasciculus (UF) which is the largest white matter pathway that connects directly temporal and frontal lobes **[6, 7]**. The UF has been implicated in several clinical DTI studies using two-dimensional regions-of-interest **[8]** which could not reliably assess the entire 3D tract **[9]**. In this report, we demonstrate using diffusion tensor tractography (DTT) of the normal-appearing uncinate fasciculus (UF) combined with whole brain lesion load measurements, the utility of DTI tractography in quantifying hallmarks of WD in relapsing-remitting MS (RRMS).

Methods: *Subjects*: We included a total of 19 right-handed healthy adult controls (13 women & 6 men; age $\mu \pm \sigma$ = 41.3 ± 9.7 years) and 19 age and gender -matched RRMS patients (see **Table 1**). The RRMS group mean and standard deviation for Expanded Disability Status Score (EDSS) = 1.55 ± 1.25, median = 2; range = 0 – 4; disease duration(DD) = 9.45 ± 7.33, median = 8.92, range = 0.17 - 25 years; whole brain lesion load percentage (lesion volume per unit intracranial volume x 100%;(LLp) = 0.6 ± 0.487 (median = 0.5; range = 0.1 - 1.7 %).

Conventional and DT- MRI Acquisition: All MRI studies were performed on a 3T Philips Intera scanner with a dual quasar gradient system and an eight channel SENSE-compatible head coil. The MRI protocol included dual-echo FSE (TE_1/TE_2/TR= 11/90/6800), FLAIR (TE/TI/TR=80/2500/80). The DTI data were acquired using a single-shot spin-echo diffusion sensitized EPI sequence with the balanced *Icosa21* encoding scheme **[10],** b=1000 sec mm^{-2}, T_R/T_E = 6100/84 msec. The slice thickness was 3.0 mm with 44 contiguous axial slices covering the entire brain; FOV=240x240 mm^2. The number of b=0 images was 8; in addition each diffusion encoding was repeated twice and magnitude averaged to enhance signal-to-noise ratio.

Data Processing: The whole brain lesion load (LL) was segmented using the FLAIR and dual echo volumes **[10].** The normal-appearing uncinate fasciculi constructed using DTI fiber tracking in DTIstudio **[11]** (see **Fig. 1**). The DTI-derived metrics include the fractional anisotropy, FA, mean or average diffusivity, D_{av}, transverse, LT, and axial diffusivities, LA, (D_{av} = (2*LT+LA)/3). Correlations between age, EDSS, DD, LL and DTI-derived metrics were computed using Spearman and Pearson coefficients. Group means, slopes and rates of change were compared using multivariate analysis.

Results: **Table 1** summarizes the DTI metrics associated with the UF on controls and RRMS patients bilaterally. In controls, the UF anisotropy was larger on the left side (p=0.03) which is explained by a strong axial leftward axial diffusivity (p=0.009). In the RRMS patients the UF diffusion asymmetry is not significant. There were no significant correlations of the UF DTI metrics and age in the healthy controls. **Table 2** summarizes the results of correlations of the UF DTI metrics with LL, DD, and EDSS on the RRMS group. Note the reduced sensitivity of anisotropy measures compared with diffusivity. Also, while the whole brain lesion load correlated strongly with the diffusivity (mean, transverse and axial) of the UF bilaterally, the EDSS correlated strongly with the diffusivities of the right UF.

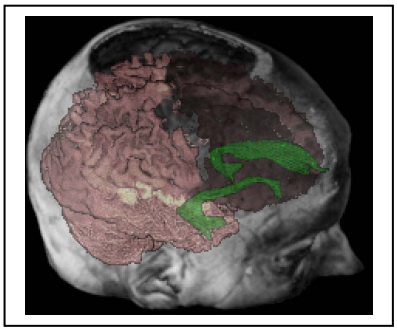

Fig 1. Illustration of the DTI tractography mapping of the uncinate fasciculus (in green)→

Table 1	Controls	RRMS	P (Controls vs. RRMS)
N (Males/Females)	19 (6/13)	19 (3/16)	
Age in years ($\mu \pm \sigma$) Range	41.3 ± 9.7 25-55.5	43.5± 7.7 25.6-55.3	0.45
Right FA	0.453±0.023	0.446±0.020	0.35
Left FA	0.463±0.026	0.457±0.028	0.53
p FA (L > R)	**0.03**	0.08	
Right Dav ($x10^{-3}$)	0.772±0.023	0.791±0.039	0.08
Left Dav ($x10^{-3}$)	0.782±0.020	0.800±0.040	0.10
p Dav(Left>Right)	**0.03**	0.20	
Right LT ($x10^{-3}$)	0.555±0.024	0.573±0.036	0.08
Left LT ($x10^{-3}$)	0.556±0.025	0.568±0.042	0.16
p LT(Left ~ Right)	0.63	0.99	
Right LA ($x10^{-3}$)	1.206±0.035	1.228±0.053	0.14
Left LA ($x10^{-3}$)	1.235±0.351	1.266±0.049	0.15
p LA(Left > Right)	**0.009**	**0.028**	

Discussion: This is the first DTI tractography study of the UF using reasonably sized cohorts of age-matched adult controls and RRMS patients that reports bilateral DTI attributes of the UF (**Table 1**). The leftward diffusion asymmetry on healthy adult controls is consistent with previous reports using ROIs **[8].** Our results in regards to reduced sensitivity of FA compared with diffusivity are concordant with previous clinical studies of stroke **[1]** and MS patients **[4, 5].** The slight increase in diffusivity in the RRMS and the strong correlation of the normal-appearing UF diffusivity metrics bilaterally with lesion load may reflect the presence of Wallerian degeneration due to the accumulative effects of lesions and neuronal/axonal damage in the frontal and temporal lobes as evidenced by reports of cortical thinning or hippocampal atrophy **[12]** as a result of lesion load. Our study shows the importance of analyzing the diffusivity metrics as potential sensitive markers of occult disease mechanisms that alter the axonal integrity **[4]**. Previous MS studies on large cohorts indicated an increase in lesion distribution in frontal, parietal and temporal lobes, respectively **[13].** The lesion activity as reflected by the whole brain LL in our study has been strongly correlated with UF diffusivity attributes and hints towards loss of axonal coherence and microstructural organization of this white matter structure.

Table 2

RRMS group Correlation r(p)	**Age**	**DD**	**LL**	**EDSS**
FA (Right UF)	-0.047 (0.847)	0.192 (0.431)	-0.249 (0.304)	-0.207 (0.395)
FA (Left UF)	0.231 (0.342)	-0.049 (0.841)	-0.315 (0.189)	-0.168 (0.491)
Dav (Right UF)	0.123 (0.616)	0.358 (0.132)	**0.686 (0.001)**	**0.581 (0.009)**
Dav (Left UF)	0.097 (0.694)	0.138 (0.574)	**0.629 (0.004)**	0.042 (0.864)
LT (Right UF)	0.112 (0.649)	0.235 (0.353)	**0.634 (0.004)**	**0.558 (0.013)**
LT (Left UF)	-0.034 (0.890)	0.114 (0.641)	**0.560 (0.013)**	0.035 (0.887)
LA (Right UF)	0.124 (0.613)	**0.496 (0.031)**	**0.649 (0.003)**	**0.494 (0.032)**
LA (Left UF)	0.298 (0.216)	0.141 (0.564)	**0.495 (0.031)**	-0.054 (0.825)

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